Implications of an Uncertainty and Sensitivity Analysis for SARS' Basic Reproductive Number for General Public Health Measures

Appendix I: Local Sensitivity Analysis of the Basic Reproductive Number

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The sensitivity analysis approach via exhaustive sampling of the parameter space provides a *global* measure of the sensitivity of model parameters. Another approach is to compute the sensitivity indices of the model parameters through local derivatives (1). This approach only provides a *local* measure as the sensitivity indices can change when the parameter values change. Here we use local sensitivity analysis to corroborate our *global* sensitivity analysis results and discuss how this approach can be applied in the analysis of cost as part of a policy of outbreak control.
Let λ represent any of the ten nonnegative parameters β, ρ, p, q, k, γ_1, γ_2, δ, α and l that define the basic reproductive number of our model (2)

$$R_0 = \left\{\beta\left[\rho + p(1-\rho)\right]\right\}\left\{\frac{q}{k} + \frac{1}{\alpha+\gamma_1+\delta} + \frac{\alpha l}{(\alpha+\gamma_1+\delta)(\gamma_2+\delta)}\right\}. \tag{1}$$

If a "small" perturbation $\delta\lambda$ is made to the parameter λ, a corresponding change will occur in R_0 as δR_0, where

$$\begin{aligned}\delta R_0 &= R_0(\lambda+\delta\lambda) - R_0(\lambda)\\ &\approx \delta\lambda \frac{\partial R_0}{\partial \lambda}.\end{aligned}$$

The normalized sensitivity index Ψ_λ is the ratio of the corresponding normalized changes and is defined as

$$\Psi_\lambda := \frac{\delta R_0}{R_0} \Big/ \frac{\delta\lambda}{\lambda} = \frac{\lambda}{R_0}\frac{\partial R_0}{\partial \lambda}. \tag{2}$$

An approximation of the perturbed value of R_0, in terms of the sensitivity index is

$$R_0(\lambda+\delta\lambda) \approx \left(1 + \frac{\delta\lambda}{\lambda}\Psi_\lambda\right) R_0(\lambda),$$

where the ten normalized sensitivity indices are

$$\Psi_\beta = 1$$

$$\Psi_\rho = \frac{\rho(1-p)}{\eta}$$

$$\Psi_p = \frac{p(1-\rho)}{\eta}$$

$$\Psi_q = \frac{q\beta\eta}{kR_0} = -\Psi_k$$

$$\Psi_\alpha = -\frac{\alpha\beta\eta}{R_0\left(\alpha+\gamma_1+\delta\right)}\left(\frac{R_0}{\beta\eta}-\frac{q}{k}-\frac{l}{\delta+\gamma_2}\right)$$

$$\Psi_{\gamma_1} = -\frac{\gamma_1\beta\eta}{R_0\left(\alpha+\gamma_1+\delta\right)}\left(\frac{R_0}{\beta\eta}-\frac{q}{k}\right)$$

$$\Psi_{\gamma_2} = -\frac{\alpha\beta\eta}{R_0\left(\alpha+\gamma_1+\delta\right)}\frac{l\gamma_2}{\left(\delta+\gamma_2\right)^2}$$

$$\Psi_\delta = -\frac{\delta\beta\eta}{R_0\left(\alpha+\gamma_1+\delta\right)}\left(\frac{R_0}{\beta\eta}-\frac{q}{k}+\frac{\alpha l}{(\delta+\gamma_2)^2}\right)$$

$$\Psi_l = \frac{\beta\eta}{R_0\left(\alpha+\gamma_1+\delta\right)}\frac{\alpha l}{(\delta+\gamma_2)},$$

with $\eta := p(1-\rho)+\rho$ and $\gamma_2 := \alpha\gamma_1/(\alpha-\gamma_1)$. For the values of the parameters used in this model, the sensitivity indices Ψ_β, Ψ_ρ, Ψ_p, Ψ_q and Ψ_l are positive, $\Psi_k = -\Psi_q$ and the remaining indices are negative. Furthermore, since all of the indices (except Ψ_β) are functions of the parameters, the sensitivity indices will change as the parameter values change.

For our specific case where $\beta = .25$, $q = .1$, $p = 1/3$, $k = .15707$, $\alpha = .2061$, $\gamma_1 = .035285$, $\gamma_2 = .0426$, $\delta = .0279$ and $\rho = .77$, and Toronto ($l = .1$) or Hong Kong ($l = .43$) the normalized sensitivity indices are computed. The sensitivity indices and the associated % changes needed to affect a 1% decrease in R_0 are given in Tables 1 and 2. Since the effective rate of patient isolation and the average rate of diagnosis are two feasible intervention strategies, we examine how changes to the parameters l and α affect the basic reproductive number (R_0). Let us first consider the outbreak in Hong Kong. The value $\alpha = .2061$ means that the mean time to diagnose an infected individual is approximately 4.85 days. The sensitivity index $\Psi_\alpha = -.1933$ means that a 5.2% increase in α, which in turn requires a decrease of 5.7 hours of mean time to diagnosis, would result in a decrease of approximately 1% in R_0. Similarly, the sensitivity index $\Psi_l = .5183$ suggests that a 1.9% decrease in the value of l, that is going from .43 to .42 isolation effectiveness[1], results in a 1% decrease in R_0. In other words, individually a 5.2% increase in α or a 1.9% decrease in l both result in approximately a 1% decrease in R_0. For the particular values of the parameters

[1]Recall that $l = 0$ corresponds to complete isolation, whereas $l = 1$ means no effective isolation occurs. Hence, a decrease in l means an increase in the effective isolation of the infected individuals.

chosen for Hong Kong, the most effective way to reduce R_0 is to decrease the transmission rate β and the parameter l (improve the effective isolation rate). In the case of Toronto, $\Psi_\alpha = -.4758$ means that a 2.1% increase in α, results in a 1% decrease in R_0, whereas $\Psi_l = .2001$ means a 5% decrease in l also results in a 1% decrease in R_0.

As can be seen from these two examples, the importance or ranking of the sensitivity indices can change as the values of the parameters change. Specifically, the sensitivity indices Ψ_l and Ψ_α satisfy the relationship

$$\|\Psi_l\| < \|\Psi_\alpha\| \qquad \Longleftrightarrow \qquad l < \frac{\delta + \gamma_2}{\alpha + 2\gamma_1 + 2\delta}. \tag{3}$$

For the particular values of the parameters given above, Figure (1) shows the level curve for the pair (l,α), where $l(\alpha + 2\gamma_1 + 2\delta) = \delta + \gamma_2$. The particular parameter values are either for Toronto $(l,\alpha) = (.1,.2064)$ or for Hong Kong $(l,\alpha) = (.43,.2064)$. Choosing the parameter values (l,α) below the level curve means that $\|\Psi_l\| < \|\Psi_\alpha\|$ and the converse is true if (l,α) is chosen above the curve. Along the level curve, the magnitude of the sensitivities is equal. Notice that the level curve divides the parameter space into two regions, each of area A_{above} and A_{below}, respectively. Since $A_{\text{above}} >> A_{\text{below}}$, Ψ_l will be the dominant sensitivity index for randomly chosen (l,α).

A significant aspect of implementing an efficient intervention policy is the fact that there are limited resources available. If one assumes, for example, that the strategies of isolation and diagnosis have associated 1% incremental costs in implementation of δC_{I} and δC_{D}, respectively, then a mixed strategy should be formulated that maximizes the effectiveness of a combined intervention. Specifically, if x denotes the magnitude of % decrease in l and y denotes the % increase in α and assuming that there is a maximum amount of total additional resources available (δC_{T}), then the total additional cost of a new mixed isolation and diagnosis intervention policy must satisfy the inequality $\delta C_I x + \delta C_D y \le \delta C_T$. Since the objective is to maximize the decrease in the reproductive number R_0, this means we want to maximize the objective function $P := \|\Psi_l\| x + \|\Psi_\alpha\| y$ under the appropriate constraints. In a more general setting, additional nonlinear constraints could be involved, in which case one would need to solve a nonlinear optimization problem. The situation where the cost of diagnosis of infected individuals may be much greater than the cost of isolation or vice versa is certainly of interest.

References

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Table 1. Sensitivity Indices for Toronto with $l = 0.1$.

Positive Sensitivity Indices		Negative Sensitivity Indices	
$\Psi_{\beta} = 1$	-1%	$\Psi_{\alpha} = -.4758$	2.10%
$\Psi_{\rho} = .6063$	-1.65%	$\Psi_{\delta} = -.1707$	5.86%
$\Psi_{l} = .2001$	-4.99%	$\Psi_{\gamma_2} = -.1208$	8.28%
$\Psi_{q} = .1172$	-8.53%	$\Psi_{k} = -.1172$	8.53%
$\Psi_{p} = .0906$	-11.04%	$\Psi_{\gamma_1} = -.1156$	8.65%

Table 2. Sensitivity Indices for Hong Kong with $l = 0.43$.

Positive Sensitivity Indices		Negative Sensitivity Indices	
$\Psi_{\beta} = 1$	-1%	$\Psi_{\gamma_2} = -.3129$	3.19%
$\Psi_{\rho} = .6063$	-1.65%	$\Psi_{\delta} = -.3016$	3.32%
$\Psi_{l} = .5183$	-1.93%	$\Psi_{\alpha} = -.1933$	5.17%
$\Psi_{p} = .0906$	-11.04%	$\Psi_{\gamma_1} = -.1216$	8.22%
$\Psi_{q} = .0706$	-14.16%	$\Psi_{k} = -.0706$	14.16%

appendix-fig1.eps

Figure 1. Level curve of (l,α) where $l(\alpha + 2\gamma_1 + 2\delta) = \delta + \gamma_2$.